Clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis

The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis

W Clark,[1] P Jobanputra,[2] P Barton[3] and A Burls[4*]

[1] Medicines Evaluation Unit, Department of Medicines Management, Keele University, UK
[2] Department of Rheumatology, University Hospital Birmingham NHS Trust, Selly Oak Hospital, UK
[3] Health Economics Facility, Health Services Management Centre, University of Birmingham, UK
[4] West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, University of Birmingham, UK

* Corresponding author

Executive summary

Health Technology Assessment 2004; Vol. 8: No. 18

Health Technology Assessment
NHS R&D HTA Programme

Executive summary

Description of technology

This report reviews the evidence of the clinical and cost-effectiveness of anakinra, an interleukin-1 receptor antagonist (IL-1Ra), for the treatment of rheumatoid arthritis (RA) in adults. Anakinra is licensed in Europe for use in combination with methotrexate, for patients with an inadequate response to methotrexate alone. Anakinra acts in the same way as naturally occurring IL-1Ra, transiently binding to the IL-1 receptor, augmenting the natural regulation of the proinflammatory effects of IL-1.

Epidemiology and background

RA is a chronic illness characterised by inflammation of the synovial tissues in joints, which can lead to joint destruction. Key aims of treatment include:

- to control symptoms of joint pain and inflammation
- to minimise loss of function and to maintain or improve quality of life
- to reduce the risk of joint damage and disability
- to treat extra-articular complications of RA
- to have well-informed and satisfied patients and carers.

RA affects around 0.5–1% of the population, with approximately 421,330 patients affected in England and Wales. Prevalence increases with age, so that prevalence at the age of 65 is six times that at 25 years. Peak age of onset is in the sixth decade and RA is more common in women than in men, by a ratio of 2.5:1.

Corticosteroids, non-steroidal anti-inflammatory drugs and analgesics are used to control symptoms, but early use of disease-modifying antirheumatic drugs (DMARDs) is key, with the aim of slowing disease progression. There are approximately eight DMARDs currently in common use in the UK. Variable effectiveness or loss of effectiveness over time and toxicity hamper their use, with low continuation rates seen over time. New DMARDs are therefore of great importance. Several new agents have appeared in recent years, including the tumour necrosis factor (TNF) inhibitors, infliximab and etanercept.

Number and quality of studies, and direction of evidence

Five randomised controlled trials (RCTs) of anakinra in adult patients with RA, involving a total of 2905 patients, of whom 2146 received anakinra, were identified. All compared anakinra with placebo and all but one presented outcome data at 24 weeks. In three trials anakinra was administered in combination with methotrexate/other DMARDs and in two as monotherapy. Only two trials evaluated the licensed dose of 100 mg daily. All five trials were identified as high quality.

Summary of benefits

The results of the clinical trials are consistent with clinical benefit (compared with placebo) as measured by American College of Rheumatology (ACR) composite response rate at 6 months. Variation in response rate was seen across the trials, which is likely to be a reflection of the size of the trials and the wide range of doses evaluated. Consistent benefit was seen at the higher dose evaluated [number needed to treat (NNT) to achieve an ACR20 response of 7, 95% confidence interval (CI) 5 to 11, at licensed dose]. Benefit was evident both with monotherapy and when used in combination with methotrexate.

Data on the efficacy end-points evaluated in a large pragmatic safety study (0757) have not been made available. This is of concern. Given the nature and scale of this study such data have the potential to alter the overall findings of this review. In the absence of data the reviewers made an educated guess about the result of trial 0757. Assuming that this trial failed to reach conventional levels of statistical significance with a p-value of treatment difference in the order of $p < 0.1$ to < 0.2, an estimate of effectiveness was derived for trial 0757. The derived estimate has been combined with the data from the earlier trials, using a random effects model, to give a best estimate about anakinra's effectiveness for ACR20 response: relative risk 1.43 (95% CI 1.16 to 1.76), risk difference 0.11 (95% CI 0.04 to 0.18), NNT 9 (95% CI 6 to 25).

Anakinra can be considered modestly effective in the treatment of RA based on ACR response.

Reduction in Health Assessment Questionnaire scores, a measure of disability, was small. Robust data on radiologically assessed joint damage are not currently available. No conclusion can therefore be made on the effect of treatment on disease progression.

Direct comparisons with other biological modifiers are not available. Adjusted indirect comparison suggests that anakinra may be significantly less effective at relieving the clinical signs and symptoms of RA, as measured by the ACR response criteria, than TNF inhibitors all used in combination with methotrexate. Such indirect results should be interpreted with caution, but can be useful in guiding clinical practice in the absence of direct comparisons between agents.

Anakinra treatment was associated with a high incidence of injection-site reactions. Serious adverse events were infrequent, but longer term follow-up is required.

Economic evaluation

Existing economic evaluations

- No fully published economic evaluations of anakinra in patients with RA were identified. Two abstract reports presented limited data.

Commentary on submitted model

- This is a Markov model with a 6 month cycle time.
- Problems associated with the structure of this model make its conclusion, that the ICER for anakinra is £16,545/quality-adjusted life-year (QALY), unreliable.

Summary of the economic analysis

The Birmingham Rheumatoid Arthritis Model (BRAM) was used to compare DMARD sequences of drugs, chosen to reflect current clinical practice, with and without the addition of anakinra at different points in the DMARD sequence. The BRAM gives a base-case estimate of the incremental cost-effectiveness ratio (ICER) of anakinra of £106,000 to £604,000/QALY. This model uses data from public domain trial results only. These recruited a highly selective patient population and may well give a more favourable estimate of cost-effectiveness than would be achieved in an average clinic population.

In the sensitivity analyses substantial variations were made in key parameters and ICERs were shown to be responsive. However, ICERs did not drop below £50,000/QALY in any univariate sensitivity analysis.

The BRAM produces an ICER for anakinra substantially higher than those for infliximab and etanercept. However, patients may respond to anakinra when they have not responded to other TNF inhibitors, as these agents have a different mechanism of action. Thus, anakinra may produce a clinically significant and important improvement in some patients that they could not otherwise have achieved.

Recommendations for research

- Current clinical trials with anakinra are of limited duration. RCTs are required to evaluate the efficacy, safety and cost of anakinra over the longer term in patients with such a chronic disease.
- Comparative trials of anakinra with other DMARDs and biological modifiers are needed to identify the comparative efficacy of these drugs and to guide clinical practice to optimise patient care.
- Trials are required to assess the role of anakinra in the treatment of patients who have failed to achieve a benefit while taking infliximab or etanercept.
- Further research is needed to assess the impact of DMARDs and anakinra on joint replacement, mortality and quality of life. Continued pharmacovigilance and analysis of potential adverse effects of new and old DMARDs are essential.
- Optimal treatment of RA may require combinations of therapeutic compounds that inhibit different mediators. Controlled clinical trials of combination therapy with two anticytokines are required to inform clinical practice, before such an approach is widely adopted.
- Suggestions that newer biological therapies reduce radiographic damage without necessarily improving clinical outcomes need to be confirmed if treatments in the absence of a clinical response are to be justified.
- Further research is needed to improve the utility of radiographic outcomes in clinical trials of RA, either by building on existing efforts with plain radiographs or through the use of newer imaging methods.

Publication

Clark W, Jobanputra P, Barton P, Burls A. The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis. *Health Technol Assess* 2004;**8**(18).

NHS R&D HTA Programme

The research findings from the NHS R&D Health Technology Assessment (HTA) Programme directly influence key decision-making bodies such as the National Institute for Clinical Excellence (NICE) and the National Screening Committee (NSC) who rely on HTA outputs to help raise standards of care. HTA findings also help to improve the quality of the service in the NHS indirectly in that they form a key component of the 'National Knowledge Service' that is being developed to improve the evidence of clinical practice throughout the NHS.

The HTA Programme was set up in 1993. Its role is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The HTA programme commissions research only on topics where it has identified key gaps in the evidence needed by the NHS. Suggestions for topics are actively sought from people working in the NHS, the public, consumer groups and professional bodies such as Royal Colleges and NHS Trusts.

Research suggestions are carefully considered by panels of independent experts (including consumers) whose advice results in a ranked list of recommended research priorities. The HTA Programme then commissions the research team best suited to undertake the work, in the manner most appropriate to find the relevant answers. Some projects may take only months, others need several years to answer the research questions adequately. They may involve synthesising existing evidence or designing a trial to produce new evidence where none currently exists.

Additionally, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme is able to commission bespoke reports, principally for NICE, but also for other policy customers, such as a National Clinical Director. TARs bring together evidence on key aspects of the use of specific technologies and usually have to be completed within a limited time period.

Criteria for inclusion in the HTA monograph series
Reports are published in the HTA monograph series if (1) they have resulted from work commissioned for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 01/62/01. The authors have been wholly responsible for all data collection, analysis and interpretation and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme, NICE or the Department of Health.

HTA Programme Director: Professor Tom Walley
Series Editors: Professor John Gabbay, Dr Chris Hyde, Dr Ruairidh Milne, Dr Rob Riemsma and Dr Ken Stein
Managing Editors: Sally Bailey and Caroline Ciupek

ISSN 1366-5278

© Queen's Printer and Controller of HMSO 2004

This monograph may be freely reproduced for the purposes of private research and study and may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising.

Applications for commercial reproduction should be addressed to NCCHTA, Mailpoint 728, Boldrewood, University of Southampton, Southampton, SO16 7PX, UK.

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.